Special article

Henri Laborit and the inhibition of action

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Henri Laborit was one of the founders of modern neuropsychopharmacology, having discovered, or participated in, the discovery of chlorpromazine, gamma-OH, clomethiazole, and minaprine. He also put forward a theory regarding the necessity of counteracting the negative consequences of defense mechanisms during anesthesia or behavioral inhibition. The scope of his work covers neurophysiology, pharmacology, psychiatry, and psychosomatics. His independence of spirit meant that most of his research was not done within university settings.

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Introduction

The French surgeon Henri Laborit is known for his work on chlorpromazine (RP4560), a molecule from the Rhône-Poulenc pharmaceutical company, synthesized at the end of 1950, and marketed as Largactil® at the end of 1952. Laborit was a man of many talents, who considered that thinking and acting in directions opposite to common beliefs (the *doxa*) was a fruitful means of making discoveries. Indeed, he made a series of significant discoveries in physiology and pharmacology. He stands among the founders of modern anesthesiology and neuropsychophamacology. He published several books on physiology and pharmacology, ethology and societal issues; he was one of the innovative thinkers of the 20th century in France. He repeatedly emphasized the fact that a better understanding of the cerebral determinants of human behaviors, such as dominance and aggression, is a necessary condition for any favorable evolution of human societies. Only two of his more than 15 books have been translated into English.[1,2] Almost all of the 624 publications listed in Medline with Laborit as author are in French. No tribute to his work has been published in English-speaking medical journals. In this article, several of Laborit's achievements will be described, and we will underline how the concept of inhibition of action might remain a worthwhile indicator for research on depression.

Brief biography

Henri Marie Laborit was born in Hanoi, French Indochina, in 1914. His father, a physician and officer in the French colonial troops, died from tetanus in 1920.

In spite of the sequelae of tuberculosis, which he had contracted at the age of 12, Laborit obtained a baccalaureate in Paris and passed the exams of the School of Naval Medicine in Bordeaux. His first practice was as a Navy physician, but, eager for better recognition, he turned to surgery. His surgical work confronted him with patients dying during or after operations, and this motivated his research in anesthesiology; this in turn led to the development of chlorpromazine, with publications in 1952.

In 1957, Laborit received the Albert Lasker Clinical Medical Research Award, together with six other researchers on reserpine and chlorpromazine. In 1958, he opened his laboratory of Eutonologie in the Boucicaut Hospital in Paris. He headed this laboratory until his death in 1995, financing his research largely with the money obtained from patenting molecules. The name *Eutonologie* means "adequate tone in all biological functions." *Figure 1* shows Laborit at his desk. He was editor in chief of the journal *Agressologie*, published from 1955 to 1983. He gave lectures in many universities, on biology but also on town planning and human behavior, and from 1978 to 1983, was invited as professor of biopsychosociology at the University of Quebec. In 1981, he received the Anokhin prize from the Soviet Union, and in 1989 he accepted the chair of the Institute of Psychosomatics in Torino, Italy. He also taught a seminar in Lugano, Switzerland, in conjunction with the University of San Diego.

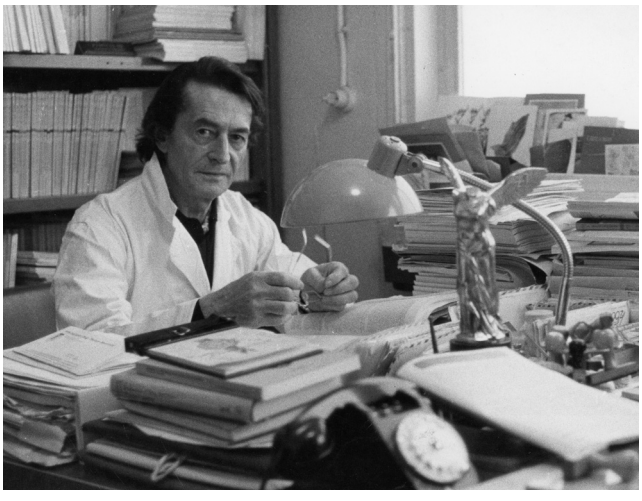

Figure 1. Henri Laborit in his laboratory. The photo was taken in the office of the Laboratoire d'Eutonologie, where Laborit spent most of his time reading scientific publications. The Victory of Samothrace statue (Lasker prize) can be seen.
Photo courtesy of: Comité français de radio télévision

From 1969 to 1976 he participated in the *Groupe des dix* (Group of ten), a series of informal discussions between French personalities in the fields of politics, biological sciences, philosophy, and sociology.

Although he was nominated for the Nobel prize, he did not receive it. It is said that this was because of the hostility of the Parisian medical microcosm, notably the dean of the Faculty of Medicine, who could not accept the new views in anesthesiology and medicine that Laborit proposed, and who made the journey to Stockholm to dissuade the jury.

Henri Laborit and his wife Geneviève had five children. His wife was an anesthesiologist, and she shared the research work in the laboratory part time, the rest of her time being spent in anesthesiology, so as to support their family financially. Indeed, Laborit only had a salary from the army and never had tenure in a French university.

Major research

In the field of pharmacology, aside from chlorpromazine, Laborit worked on or discovered the neurotransmitter gamma-OH, the antidepressant minaprine, the sedative clomethiazole.

In the field of anesthesiology, Laborit studied a mix of an opiate analgesic and a hypnotic of the antihistamine class in order to induce a pharmacological disconnection of the neurovegetative system.[3] He considered that the nonspecific responses to stressors were in themselves toxic to the body: patients died in shock not because their defenses were exhausted, but because giving adrenaline to treat hypotension increased the dangers of the stress responses. He wanted to shut down the stress response, since he saw that patients were killed by the endogenous mechanisms supposed to protect them from shock. This worked well, but made him a medical heretic to his colleagues! The *Laborit cocktail* or *cocktail lytique* was the combination of promethazine, pethidine, and chlorpromazine, and this was later called neuroleptanalgesia. During surgical procedures, the patients were calm, still capable of obeying simple orders, and had fewer variations of blood pressure, although this effect of surgery did persist.

Laborit developed further the technique of hypothermia, associated with chlorpromazine, and concluded that this provided protection against the toxicity of stress responses during anesthesia and surgery.

The indifference observed under chlorpromazine led to trials in agitated patients, by a small group of psychiatrists, advised by Laborit. Jean Delay and Pierre Deniker described the effects of the molecule in manic psychosis and mental confusion.[4]

Laborit also worked on the toxicity of oxygen. He was asked to do this by the army because of the toxicity of oxygen in divers. The synthesis of gamma-OH emerged this work, with the intention of finding a γ-aminobutyric acid (GABA)-like compound that would cross the blood-brain barrier. The idea was that since glial cells had few mitochondria, and neurons had many, the former helped the latter, and neurons could be indirectly helped by facilitating the pentose pathway in glial cells. This was a precursor in the field of free radical research and therapy. Gamma-OH was used in delirium tremens, in anesthesia after head trauma, in insomnia, and is still prescribed in narcolepsy.

The antidepressant Agr 1240 (minaprine, marketed as Cantor® until 1990) was a stimulating molecule that Laborit developed with the idea of neutralizing the consequences of inhibition of action.

Inhibition of action

A major role of the brain is to organize behaviors, ie, action. There is inhibition of action when behaviors become impossible, and this is deleterious to health. This happens when an instinctive behavior (such as fight or flight) is impossible, when acting is useless, when a danger cannot be predicted, or when no previous response pattern exists to direct action. In these situations, a brain system, the *système inhibiteur de l'action*, or behavioral inhibition system (BIS), is activated and stimulates the neuroendocrine responses that were described by Walter Cannon in the 1920s and Hans Selye in the 1930s and 1940s.

Inhibition of action is illustrated in animal experiments that we carried out in Laborit's laboratory during the early 1970s. Rats were placed in an activity-avoidance conditioning apparatus with two compartments. Rats received 10 cycles of 21 plantar electric shocks daily for 1 week, each shock session being preceded by a light and sound warning stimulus. In these conditions, if the animal could carry out an active avoidance (when the other compartment was open), or if the rat was placed with another rat and could fight with it, no arterial hypertension was observed. If the rat could not escape or fight, hypertension developed that remained chronic for 1 month.[5] Follow-up of these rats showed that they remained hypertensive 3 months later (Kunz, unpublished). In another experiment, all rats received shocks from which they could not escape. Half of them were subjected to convulsions (induced electrically) after each shock session and did not develop hypertension. This lack of hypertension was interpreted as being due to the impossibility of conditioned learning because of the convulsions.[6] The BIS (median septal area, hippocampus, lateral amygdala and ventromedial hypothalamus) could be at the origin of peripheral vasomotor disorders, while the central activating systems, or behavioral activating systems (BAS—medial forebrain bundle and paraventricular system) would prevent these effects.

A film was made based on Laborit's theories: *Mon Oncle d'Amérique (My American Uncle)* by the French film maker Alain Resnais (1980). The film contains explanations by Laborit *(Box 1)*,[7] as well as scenes of the rat experiments described above. The main theme of the movie was that achieving the right equilibrium between action and inhibition of action is paramount to mental and physical health. Fleeing is the solution to escape inhibition of action, when other behaviors are not possible.

Discussion

Responses to one's environment, when dysfunctional, become toxic, as Laborit studied in the 1950s in the field of anesthesia. He later studied the behavior of rats and concluded that inhibition of action induced pathogenic mechanisms. He observed that humans have ancestral instinctive behavioral responses that are not adapted to the modern societal milieu. His aim was to explain biology and behavior at each of the different levels of functioning, from cell to society.

The concept of inhibition of action remains operative in the search for new psychotropic medications, which could counterbalance unfavorable endogenous defense reactions. ❑

Acknowledgments: My work in the Eutonology laboratory was made fruitful and greatly enjoyable by the presence and collaboration of Henri Laborit, Geneviève Laborit, Claire Baron, Catherine Ferran, Josiane Laurent, Françoise Thuret, and Bernard Weber.

Box 1

Mon Oncle d'Amérique (My American Uncle)

In this 1980 movie by Alain Resnais, Laborit explains several of his ideas. The film was a success, but some critics considered Laborit's declarations to be too reductionist.

A being exists only in order *to be*. That is, to maintain its structure, to remain alive. […] Animals […] have to act within a space. And to do this, they need a nervous system. This nervous system allows the animal to act within and on the environment, always with the same purpose - to *ensure survival*. […]
The purpose of a brain is not to think, but *to act*.
[…] There is a first brain, which MacLean called *reptilian*, the brain of reptiles. It triggers behaviors associated with immediate survival, without which the animal could not survive […]
A second brain is added to the first and is usually called the brain of *memory*. Without a memory of what is pleasant or unpleasant, there is no way of feeling happiness, sadness, distress, anger or love. We could almost say that "a living being is a memory that acts."
A third brain is added to the first two: the *cerebral cortex*. In humans it has developed considerably and is called the *association cortex*. What does this mean? It means that this third brain associates the underlying neural pathways, which bear the trace of past experiences, and combines them differently from the way they were imprinted by the environment at the time of the experience itself. Humans, that is, are able *to create*, to generate *imaginary* processes. […]
So, these are our three brains. The first two operate *unconsciously* - we do not know what they have us *do*. These are the instinctive urges, cultural reflexes. The third brain gives us an explanatory language, which always provides an excuse, an alibi, for the unconscious functioning of the first two brains.
[…] One can distinguish four main types of behaviors. The first is the behavior of *consumption*, that satisfies basic needs. The second is a behavior of *gratification*—when we experience an action that yields pleasure, we try to repeat it. The third is a behavior in response to punishment, either by *flight* to avoid it or by *fight* to destroy the source of aggression. The last is a behavior of *inhibition*: no movement, tense waiting, rising anxiety. Anxiety marks the impossibility of mastering a situation. […]
When two individuals have different plans or the same plan and compete to carry it out, there is a winner and a loser. One of the individuals becomes dominant over the other. Seeking *dominance*, in a space one can call the territory, is the fundamental basis of all human behaviors, the motivation of this being wholly unconscious.
So there is no *property* instinct; nor is there a *dominance* instinct. There is simply the process whereby, through the nervous system, the individual learns to keep for himself an object or a being that is also wanted, coveted by another being. And the individual knows, through this learning process, that in this competitive situation if he wants to hold onto the object or being, he must dominate. […]
Through language humans have been able to transmit from generation to generation all the experience they have acquired over millennia […] In other words, our instinctive urges and our cultural reflexes will be masked by language, by a logical argument.
Language therefore helps hide the cause of dominance, the underlying mechanisms, and the establishment of dominance. It makes the individual believe that by working for the common good he will experience his own pleasure. Whereas, in general, all he does is to maintain hierarchical situations that are obscured by linguistic alibis, which in a way serve him as an excuse. […]
Among humans, social laws generally proscribe defensive violence. The construction worker who every day sees a site foreman he detests can't punch him in the face, because someone will call the police. So *fight* is not an option. But neither is *flight*. He can't quit because he'd be unemployed and every day of his life, every week in the month, every month in the year, as the years go by, he is subject to *inhibition of action*. A person has ways

of escaping this *inhibition of action*, by aggressiveness. This is never motiveless; it is always a response to *inhibition of action*. This leads to an explosion of aggression which is rarely productive but which, in terms of the nervous system, is perfectly explicable.
So, it's worth repeating, this situation in which an individual can find himself, this *inhibition of action*, if it persists, induces pathological situations. The biological perturbations accompanying it will trigger physical diseases and all the behaviors associated with mental illness. […]
The unconscious mind is a fearsome instrument. Not so much because of its repressed content […] but because of everything that is, on the contrary, authorized (reward) and sometimes even rewarded by the social culture that has been implanted in the brain since birth, of the presence of which the person is unaware. Yet it is the unconscious that guides this person's actions […]
What is called the personality is constructed from a mishmash of value judgments, prejudices, and commonplaces which weigh heavily and which, with age, become ever more inflexible, increasingly unquestioned. And when a single brick in the edifice is removed, when the edifice collapses and the person discovers anxiety, then this anxiety will express itself even if it means murder, in the case of an individual, or genocide or war, for social groups. Here we begin to understand by what mechanisms, why and how, through history and in the present, hierarchical scales of *dominance* are established.
As long as people on this planet remain unaware of how their brain works and how they use it, as long as it has not been said that hitherto it has always been to *dominate* others, there is little chance that anything will change.

Henri Laborit y la inhibición de la acción

Henri Laborit fue uno de los fundadores de la moderna neuropsicofarmacología al descubrir o participar en el descubrimiento de la clorpromazina, el gama-hidroxibutirato, el clometiazol y la minaprina. Él también adelantó una teoría relacionada con la necesidad de contrarrestar las consecuencias negativas de los mecanismos de defensa durante la anestesia o inhibición conductual. El alcance de su trabajo se extiende a la neurofisiología, la farmacología, la psiquiatría y la psicosomática. Su independencia de espíritu se tradujo en que la mayor parte de su investigación la realizó fuera de los ambientes universitarios.

Henri Laborit et l'inhibition de l'action

Henri Laborit fut l'un des pères fondateurs de la neuropsychopharmacologie moderne. Il a découvert, ou participé à la découverte de molécules telles que la chlorpromazine, le gamma-OH, le clomethiazole, et la minaprine. Il est également à l'origine d'une théorie sur la nécessité de neutraliser les effets négatifs des mécanismes de défense pendant l'anesthésie ou l'inhibition comportementale. Ses travaux ont porté sur des domaines aussi variés que la neurophysiologie, la pharmacologie, la psychiatrie et la psychosomatique. Jaloux de son indépendance, il a effectué la plupart de ses recherches hors du cadre universitaire.

REFERENCES

1. Laborit H. *Stress and Cellular Function*. Philadelphia, PA: Lippincott; 1959.
2. Laborit H. *Decoding the Human Message*. London, UK: Allison and Busby; 1977.
3. Laborit H, Huguenard P, Aullaume R. Un nouveau stabilisateur végétatif (le 4560 R.P.). *Presse Méd*. 1952:60:206-208.
4. Delay J, Deniker P, Harl JM. Utilisation en thérapeutique psychiatrique d'une phénothiazine d'action centrale élective. *Annales Médico-Psychologiques*. 1952;110:112-117.
5. Kunz E, Valette N, Laborit H. Rôle de l'apprentissage dans le mécanisme d'inhibition comportementale et de l'hypertension artérielle consecutive à l'application de stimulus aversifs sans possibilité de fuite ou de lutte. *Agressologie*. 1974;15:381-385.
6. Kunz E, Valette N, Laborit H. Rôle antagoniste de l'activité motrice d'évitement ou de lutte à l'égard de l'hypertension artérielle chronique provoquée chez le rat par l'application journalière d'un choc électrique plantaire. *Agressologie*. 1974;15:333-339.
7. Resnais A. *Mon Oncle d'Amérique*. 1980. DVD version: MK2; 2008.